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Original Article

Nivolumab in relapsed/refractory Hodgkin lymphoma: towards a new treatment strategy?

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Abstract: Chemo-refractory Hodgkin lymphoma (HL), especially after failure of high-dose therapy and autologous stem cell transplantation (ASCT), has a very poor prognosis. Nivolumab, an anti-PD-1 monoclonal antibody, demonstrated durable responses and manageable toxicity in a significant proportion of HL patients who fail both ASCT and brentuximab vedotin. Although anti-PD-1 treatment is often well tolerated, immune-related adverse events (iAE) were frequently observed. New perspectives could be represented by treatment discontinuation in patients with prolonged response or toxicity with the possibility of a re-treatment at relapse, subsequent chemotherapy or a modification of the dose-intensity or treatment duration. The efficacy of anti-PD-1 re-treatment was demonstrated in several cases and we have successfully managed 1 case with this strategy. With the main aim of avoiding the relapse-related psychophysical stress for the patient with manageable toxicity, we have successfully administered nivolumab every 4 weeks to 3 patients in prolonged complete remission, who presented with iAE during treatment. We believe that nivolumab should not only represent a bridge to allogeneic SCT, but it may play an important role also beyond the approved indication and current standard clinical care.

Keywords: Hodgkin lymphoma, nivolumab, prognosis

Introduction

Chemo-refractory Hodgkin lymphoma (HL), especially after failure of high-dose therapy and autologous stem cell transplantation (ASCT), has a very poor prognosis, although new drugs that have recently become available can offer salvage options [1].

Programmed Death 1 (PD-1) ligands, PD-L1 and PD-L2, can engage the PD-1 receptor on T-cell surface and induce a reversible T-cell inhibition, the so-called T-cell "exhaustion" [2, 3]. Since the abundant PD-L1 and PD-L2 expression on the surface of neoplastic Reed-Sternberg cells and its crosstalk with PD-1 expressed on T-lymphocytes limits immune response and favors tumor growth and survival, the inhibition of this immune-escape pathway emerged as a very promising approach. Moreover, PD-L1 and PD-L2 genes are involved in the chromosome 9p24.1 amplification, a commonly reported genetic alteration in HL cases. The coamplification of PD-L1 and PD-L2 genes on chromosome 9p24.1 suggests the best treatment strategy could be represented by the blockade of common PD-1 receptor on T-cell surface rather than selective ligand blockade [2, 3].

Nivolumab, a fully human IgG4 anti-PD-1 monoclonal antibody, previously successfully used in malignant melanoma and other solid tumors, was the first so called "Check Point Inhibitor" (CPi) to demonstrate durable responses and manageable toxicity in a significant proportion of HL patients who fail both ASCT and brentuximab vedotin (BV) [4, 5]. In the initial report of phase II CheckMate 205 study, 80 relapsed/refractory (R/R) HL patients who failed both ASCT and BV received nivolumab 3 mg/Kg every 2 weeks; overall response rate (ORR) was 66.3%, complete response (CR) rate was 9%, with a median progression-free survival (PFS) of 10 months [4]. At the end of the study, which enrolled 243 patients, ORR was 69%, median duration of response (DoR) and PFS were 16.6 months and 14.7 months, respectively [5]. No

treatment-related deaths were reported, confirming treatment efficacy and safety in this subgroup of patients with a very poor prognosis [5].

It's now evident that nivolumab represents a very strong weapon in the "therapeutic arsenal" for R/R HL, but several questions to define its optimal role are still unanswered. Nivolumab is approved in R/R HL patients who failed both BV and ASCT, until progressive disease (PD); since DoR and PFS unfortunately don't suggest a curative strategy, the majority of hematologists consider its optimal role as a "bridge" to allogeneic-SCT (allo-SCT) [5, 6]. Although anti-PD-1 treatment is often well tolerated, immune-related adverse events (iAE) were frequently observed and this is particularly evident when CPi are used after allo-SCT, with a frequent onset of severe and often treatment-refractory graft versus host disease (GVHD) [5-7]. FDA published specific treatment recommendations and warning about nivolumab in the context of allo-SCT, with the advice to carefully weigh risks and benefits [6]. In a real-life experience 39 out of 74 R/R HL patients received allo-SCT after a median of 8 nivolumab doses, grade 2-4 acute GVHD was 33.3% [7]. Due to the small sample size and different characteristics between patients treated with or without allo-SCT, this trial cannot give a clear answer on the survival benefit of allo-SCT after nivolumab.

Furthermore, available data showed a significant proportion of patients receiving nivolumab remains in CR without consolidation, raising the question whether in all cases the drug should be considered as bridge to allo SCT and/or until PD [5-7].

New perspectives could be represented by treatment discontinuation in patients with prolonged response or toxicity with the possibility of a re-treatment at relapse, subsequent chemotherapy or a modification of the dose-intensity or treatment duration. In a retrospective trial, out of 24 HL cases with PD after anti-PD-1 therapy (most of them receiving nivolumab, median PFS 7.5 months), 17/24 received chemotherapy alone and 7/24 a combination therapy. Response after re-exposure to chemotherapy was satisfactory, ORR was 67% and CR rate was 42%; median PFS was 11 months, arguing the possibility to restore a chemosensitivity in previously chemo-refractory patients [8].

The recently published paper by Manson and colleagues, as illustrated in **Table 1**, demonstrated the efficacy of anti-PD-1 re-treatment in 7 HL patients (6 patients treated with nivolumab and 1 patient with pembrolizumab) who experienced disease relapse after anti PD-1 discontinuation because of durable remission or toxicity. Remarkably, 4 out of 7 cases obtained ongoing responses after a median follow-up of 19.2 months from re-treatment [9]. We strongly agree with the authors about the possibility to remain "anti-PD-1 sensitive" and to successfully receive a second course of the same agent at relapse.

In our clinical practice, we have successfully managed 1 case with the same treatment strategy. The patient was refractory to 3 lines of therapy, including BV. Briefly, nivolumab was initiated in an Expanded Access Program and a durable CR was achieved without significant toxicity. Expanded Access Program was approved by Comitato Etico Regione Toscana-Area Vasta Sud-Est. After 18 months we decided to discontinue nivolumab and to perform ASCT as consolidation. Unfortunately, 6 months after ASCT the patient relapsed; due to the unavailability of nivolumab, not yet approved in Italy, we administered 5 doses of BV, but the patient experienced B-symptoms and PD at CT scan. Following drug approval, the patient was re-treated with nivolumab, with the new dosage indicated in the data sheet of 240 mg every 2 weeks; B-symptoms rapidly disappeared and CT scan after 3 months showed a CR. Treatment is ongoing to date and CR was maintained at last evaluation, 20 months since re-treatment.

Fedorova and colleagues enrolled 23 R/R HL patients who discontinued nivolumab in CR; after discontinuation, 2-y PFS was 55.1% and median time to relapse was 11 months. Out of 11 cases who received re-treatment, ORR was 67% (CR rate 33%) and median PFS was 16.5 months; all patients were alive at last evaluation [10].

With the aim of avoiding disease relapse with limited toxicity, including financial toxicity, low-dose nivolumab and/or prolonged treatment interval have been successfully investigated,

Table 1. Clinical results of anti PD-1 re-treatment or continuous treatment with reduced dose intensity

	Manson and colleagues	Fedorova and colleagues	Chan and colleagues	Lepik and colleagues
Patient population	HL R/R, 4-11 prior lines	HL R/R, 3-10 prior lines	HL R/R, 1-7 prior lines	HL R/R 2-7 prior lines
Treatmentstrategy	Re-treatment	Re-treatment	Low-dose	Low-dose
Number of patients	7	11	17	30
Regimen	Standard doses of nivolumab (N=6) or pembrolizumab (N=1)	Nivolumab 3 mg/Kg every 2 weeks	Pembrolizumab (N=11) 100 mg every 3 weeks or nivolumab (N=6) 40 mg every 2 weeks	Nivolumab 40 mg every 2 weeks
ORR (%)	100%	67%	100%	70%
CR (%)	57.1%	33.3%	73% for pembrolizumab, 67% for nivolumab	43.3%
Grade 3-4 iAE	Hypereosinophilia, grade 4 liver acute GVHD, 1 case each	1/11 (9.1%)	None	10% and included arthralgia (gr 3), pneumonitis (gr 4) and increased ALT/AST (gr 4)
Survival	Median follow-up 19.2 months, 4 out of 7 patients have ongoing responses	Median PFS 16.5 months, OS 100% at last follow-up	Median PFS 35 months for pembrolizumab, 33 months for nivolumab, median OS not reached	Median PFS 18.4 months. After a median follow-up of 19.2 months, 96.7% of patients were alive

Abbreviations: HL, Hodgkin lymphoma; R/R, relapsed/refractory; ORR, overall response rate; CR, complete response; iAE, immune-related adverse events; GVHD, graft versus host disease; PFS, progression-free survival; OS, overall survival.

as summarized in **Table 1**. Promising findings were obtained with nivolumab 40 mg every 2 weeks by Lepik and colleagues; CR rate was 43.3%, median PFS was 18.4 months and grade 3-5 AE were reported in only 4/30 patients [11]. Another recent report showed an ORR of 100% in a cohort of 17 R/R HL cases receiving pembrolizumab 100 or 130 mg every 3 weeks (N=11) or nivolumab 40 mg every 2 weeks (N=6), with prolonged PFS and manageable toxicity, including iAE [12].

At our Institution, with the main aim of avoiding the relapse-related psychophysical stress for the patient with manageable toxicity, we have administered nivolumab every 4 weeks to 3 patients in prolonged CR, who presented with iAE during treatment. All procedures performed were in accordance with the ethical standards of our Institution. All patients gave written informed consent in accordance with the Declaration of Helsinki and its amendment.

The first patient developed grade 2 arthralgia after 8 months of treatment with nivolumab 240 mg every 2 weeks, CT scan showed a CR, thus we decided to administer therapy every 4 weeks. Arthralgia disappeared and the patient maintained CR at last CT evaluation after 18 monthly infusions. The second case developed grade 2 back pain with diagnosis of sacroiliitis at CT scan performed after 39th nivolumab administration. Since CT scan showed a CR, we administered therapy every 4 weeks, back pain disappeared and subsequent CT showed disappearance of sacral inflammation without disease relapse; CR was maintained after 18 monthly infusions. The third patient experienced exacerbation of a previously diagnosed psoriasis after 22 nivolumab cycles; since CT scan showed a CR, we started to administer therapy every 4 weeks, psoriatic skin lesions rapidly improved and CR was maintained after 18 monthly infusions.

Based on this experience, we suggest treatment administration every 4 weeks for patients achieving a prolonged CR after nivolumab administration every 2 weeks is effective and feasible, with significant cost savings and limited toxicity. We believe that different modalities to manage patients with long-lasting CR are conceivable, such as a sort of maintenance strategy and a retreatment at disease relapse, with the common aim of reducing iAE while ensuring significant savings for national health service.

In conclusion, nivolumab has undoubtedly improved the prognosis of R/R HL, especially in chemo-refractory patients or in cases who failed ASCT. We believe that this drug should not only represent a bridge to allo-SCT, but it may play an important role also beyond the approved indication and current standard clinical care. Finally, we are confident in further studies aimed to define the optimal dose and all the unexplored possibilities of this fundamental drug.

Disclosure of conflict of interest

None.

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